Contemporary Endocrinology: G-Proteins, Receptors and Disease

Edited by Allen M. Spiegel

Humana Press, $135, 336 pp.

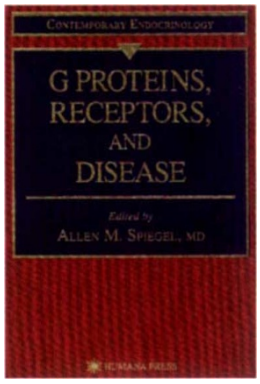
ISBN: 0-896-03430-5, 1998

REVIEWED BY GRAEME R. MARTIN
Head, Department of Molecular Pharmacology
Center for Biological Research
Roche Bioscience R2-101
3401 Hillview Avenue
Palo Alto, CA 94304 USA

G-protein coupled receptors (GPCRs) have a long established reputation as attractive targets for drug discovery and are substrates for some of the most important medicines currently available. Traditional approaches to these targets have been pragmatic—the aim being simply to mimic or block the actions of the endogenous hormone in an attempt to regulate activity in a gross fashion. Today however, the exploration of receptor function and signaling at a molecular level provides mechanistic insights into an array of diseases, most notably those resulting from structural mutations of an ion channel, a transmembrane receptor or a G-protein. This new-found knowledge has advanced therapeutics on two fronts. First, it provides a basis for disease definition and diagnosis. Second, it identifies more subtle means by which pharmacological intervention might more effectively modulate receptor-effector coupling to normalize an imbalance of receptor signaling.

In *G-Proteins, Receptors and Disease* this sea-change in approach to modern therapeutics comes over strongly in a series of chapters discussing endocrine diseases caused by a loss or gain of function in GPCRs. In the majority of diseases discussed, specific mutations in the receptor or the subunit of the associated G-protein induce a change in GPCR signaling. Consequently, loss or gain of function results either from an altered ability of the receptor to recognize ligands, or more intriguingly, from a change in receptor constitutive activity: that is, the ability of the receptor to signal in the absence of ligand, as in some cases of hyperthyroidism. The demonstration of this behavior in a physiological setting validates observations of receptor behavior made in recombinant receptor-effector systems.

This book also highlights the fact that although the pathophysiological consequences of altered GPCR signaling have long been recognized in terms of a clinical diagnosis, it is only during the last five to ten years that a molecular 'diagnosis' has become possible. However, the chapters do not lose themselves in the detail of this molecular revolution, but rather retain the clinical perspective, providing a valuable continuum between the preclinical and clinical science pertaining to each disease. This balanced coverage of modern basic and clinical research should make this book equally appealing to students, medical practitioners seeking a state-of-the-art synopsis of GPCR-mediated endocrine disorders and researchers looking to capitalize on new approaches to drug therapy.



Although the running order of chapters is logical, it is frustrating that no effort has been made to organize them into thematic groups. A concise, but sufficient introduction provides a clear outline of the biochemistry of GPCR signaling and briefly considers diseases known to result from altered signaling. This is followed by in-depth coverage of diseases associated with G-protein mutations as well as diseases associated with receptor mutations. In each of these categories, at least two chapters deal with pre-clinical approaches using gene deletion or mutation strategies to define pathophysiological roles for specific G-proteins or GPCRs. The approaches discussed are forward-looking and include the development of inducible, tissue-specific promoters to provide knock-down of target proteins in cases where gene inactivation through homologous recombination would otherwise be lethal. In the remaining chapters, the emphasis is given to diseases defined by clinical diagnosis and subsequently found to result from a G-protein or GPCR mutation. The last contribution in the book covers an association analysis of β_3-adrenoceptor polymorphism and obesity, which although an interesting chapter in itself, stands alone in a book where the genetics of heritable disease is not the main thrust.

All in all, *G-Proteins, Receptors and Disease* is a volume worthy of a place on the bookshelf of anyone with a current interest in endocrine disease and GPCR-targeted approaches to therapeutics. At a time when the term genomics is abused as much as it is used in defining current avenues of biomedical research, it is refreshing to find a book that communicates just how much genomics-based research can accelerate understanding, not just of a discrete area of science, but of human disease.

Genetics, Society and Clinical Practice

By P. S. Harper & A. J. Clarke

BIOS Scientific Publishers, £19.95, 264 pp.

ISBN 1-859962-068, 1997

REVIEWED BY ARNO G. MOTULSKY
University of Washington
Department of Medicine and Genetics
RG-25
Seattle, WA 98195-0001

The two British authors of this book, both from the Institute of Medical Genetics at the University of Wales, have been frequent contributors to the expanding literature dealing with socio-ethical problems in medical genetics. Peter Harper is a well known medical geneticist who has made many contributions to various areas of clinical genetics. Angus Clarke, who also is a physician/geneticist, has been particularly interested in the impact of genetic disease on patients and on society in general.

Societal and ethical problems of medical genetics are often discussed by bioethicists and lawyers. Molecular biologists who write about medical implications often oversimplify the intricacies of complex diseases and it is therefore helpful that practicing clinical geneticists offer their views. Physicians, non-medical biological scientists and epidemiologists will all find this book useful and it is a must for medical geneticists and genetic counselors who will gain an informed and critical view of their field from the book.

Many of the author's previous essays have been brought up to date in this book, which comprises four sections dealing with genetic testing, genetic screening, general issues in genetics, and abuse of genetics (past, present and future). While the authors describe the